



The Latest on Uveal Melanoma Research and Clinical Trials: Updates from the Cure Ocular Melanoma (CURE OM) Science Meeting (2019)

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ABSTRACT

Uveal melanoma is a rare cancer in adults, but its treatment is one of the clinical unmet needs in the melanoma field. Metastatic disease develops in approximately 50% of patients and is associated with poor survival due to the lack of effective treatment options. It provides a paradigm for cancers that show evidence of aberrant G protein–coupled receptor signaling, tumor dormancy, and liver-selective metastatic tropism and are associated with the loss of the BAP1 tumor suppressor. At the Melanoma Research Foundation CURE OM Science Meeting at the Society for Melanoma Research Meeting held in Utah on November 20, 2019, clinicians and researchers presented findings from their studies according to three themes within uveal melanoma: (i) ongoing clinical trials, (ii)

molecular determinants, and (iii) novel targets that could be translated into clinical trials. This meeting underscored the high interest in the uveal melanoma research field and the unmet need for effective treatment strategies for late-stage disease. Findings from ongoing clinical trials are promising, and multiple studies show how novel combinatorial strategies increase response rates. Novel targets and tumor vulnerabilities identified bioinformatically or through high-throughput screens also reveal new opportunities to target uveal melanoma. The future directions pursued by the uveal melanoma research field will likely have an impact on other cancer types that harbor similar genetic alterations and/or show similar biological properties.

Introduction

Uveal melanoma is the most common intraocular malignancy in adults. It represents about 5% of all melanoma diagnoses in the United States and has an incidence of approximately 2,000 cases per year (1). Primary disease can be successfully treated with local therapy; however, approximately 50% of uveal melanoma cases metastasize with high propensity (90%) to the liver (2). Overt metastases often take years or even decades to develop, highlighting the likelihood of early dissemination of tumor cells from the primary site and cellular dormancy (3). Therapeutic options for advanced-stage disease have been underwhelming to date. Immune checkpoint inhibitors, which have revolutionized treatment in skin melanoma and other tumors, have less efficacy in uveal melanoma with the best overall response rate (ORR) of 18% (4). The need for clinical trials in the field of uveal melanoma and the exploration of new targets and therapeutic agents was particularly emphasized at this meeting.

Clinical Trials in Uveal Melanoma

The first session of the meeting was chaired by Sapna Patel (MD Anderson Cancer Center, Houston, TX) and focused on ongoing clinical trials. Responses of uveal melanoma to combined immune checkpoint inhibitors (anti-PD1 and anti-CTLA4) are not comparable with those in cutaneous melanoma (4); hence, there is a need to optimize strategies using immune-based therapies. Dr. Suthee Rapi-suwon (Georgetown University Medical Center, Washington, DC) presented the phase II trial of adjuvant ipilimumab in combination with nivolumab for high-risk patients with locally treated uveal melanoma. The primary endpoint is 3-year relapse-free survival with a goal to reduce development of distant metastasis following primary tumor treatment. Adjuvant therapies including immune checkpoint blockades are being tested in high-risk cancers but uveal melanoma was excluded; hence, this study will be important to compare with other immune checkpoint inhibitor adjuvant studies in other tumor types. There is precedent for the evaluation of agents in the adjuvant setting that demonstrate little benefit in metastatic disease. One example is the previous approved use of recombinant IFN α 2a for cutaneous melanoma in the adjuvant setting (5). In tumor types that are not classically responsive to immune therapy in the metastatic setting, it will be important to understand if augmenting immune response in the minimal residual disease setting is beneficial.

Clinical trials by Dr. Takami Sato (Thomas Jefferson University, Philadelphia, PA) have shown encouraging results with tebentafusp (IMCgp100), a bispecific antibody that redirects CD3⁺ T cells to gp100-expressing melanoma cells, such as uveal melanoma, inducing cytotoxicity. ORR was 18% in phase I (6). In the phase II expansion cohort studying patients with prior treatment, a major area of focus is whether tebentafusp can restore sensitivity to the immune checkpoint inhibitors in metastatic uveal melanoma (7). A separate trial of tebentafusp compared with investigator's choice treatment in previously untreated patients is ongoing. New strategies to overcome resistance to immunotherapy was also discussed by Dr. Filip Janku (MD Anderson Cancer

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Center, Houston, TX). He noted that a type I IFN signature is associated with benefit from ipilimumab in melanoma (8) and then expanded on phase I trials to target a type I IFN response. Such trials include the use of intratumoral stimulator of IFN gamma agonists and intratumoral toll-like receptor agonists.

Liver metastasis is common in uveal melanoma and liver resection is often not feasible. Many of the ongoing uveal melanoma trials focus on liver-directed therapy coupled with anticancer and immune-based therapies. Given that the majority of death in uveal melanoma is from liver failure, and that liver-directed therapy is associated with a survival benefit (9) not only in uveal melanoma but also in other solid tumors, this is a reasonable approach to continue to explore alone and in combination with systemic therapy (10). Dr. Meredith Pelster (MD Anderson Cancer Center, Houston, TX) presented on liver-directed therapy with Yttrium-90 (Y-90) radioembolization in combination with systemic ipilimumab and nivolumab. Potential for synergy with this combination was reported previously where median overall survival (OS) was prolonged to 26.5 months compared with 9.5 months in patients treated with Y-90 only (11, 12). The study presented by Dr. Pelster was a further investigation of this synergy. Initially, the triple combination therapy induced liver toxicity but with Y-90 and immunotherapy dosage adjustments, toxicity was found to be more manageable. Currently, durable responses have been seen including one patient with complete response of 25 months and 2 patients with partial response of 12 and 16 months. This study continues to recruit patients. Sapna Patel (MD Anderson Cancer Center, Houston, TX) talked about the phase Ib trial using percutaneous injection of hepatic intratumoral PV-10, a liver-directed therapy with a solution of Rose Bengal, a small molecule which accumulates in tumor lysosomes triggering autolysis. The study allows concomitant use of standard of care immune checkpoint blockade in hopes to propagate the effects of immunogenic cell death. In 13 patients, stable disease was achieved in 62.5% and partial responses in 37.5% of the patients. Further follow-up is needed to calculate the survival benefit with this approach. Dr. Zeynep Eroglu (Moffitt Cancer Center, Tampa, FL) presented on Percutaneous Hepatic Perfusion (PHP) with melphalan, which delivers a high concentration of chemotherapy (melphalan) into the liver. Contemporary retrospective analysis of outcomes in patients indicated an ORR of 47%, median progression-free survival (PFS) of 8.1 months, and 1-year OS of 64.6% (13). The phase III FOCUS trial, a single-arm and multicenter study (PHP-melphalan administered every 6–8 weeks in patients with metastatic uveal melanoma) is open and recruiting patients.

MEK inhibitors were suboptimally efficacious in advanced stage uveal melanoma, highlighting the need for new targeted therapy trials (14). One target discussed was protein kinase C (PKC) which acts downstream of Gαq/11 proteins (15). Dr. Meredith McKean (Sarah Cannon Research Institute, Nashville, TN) spoke about a trial with a dedicated uveal melanoma cohort for a second-generation PKC inhibitor, LXS196, which was shown to be effective in preclinical studies. A key future avenue is to analyze the tolerability of LXS196 in combination with additional kinase inhibitors.

Like in other cancers, in uveal melanoma, the threshold for activity that is considered promising should be deliberated in the context of past results. Benchmarks for a promising therapy should exceed the outcomes of a recent meta-analysis of metastatic uveal melanoma from 29 trials. In that report analyzing trials from 2000 to 2016, the median PFS was 3.3 months, 1-year OS was 43%, and median OS is 10.2 months (16). In addition, therapies that induce an objective response rate greater than 15% and with consistent benefits (e.g., durable responses) have been recognized by federal agencies as worthy

of further investigation. As an orphan disease, federal agencies are also willing to consider nonrandomized trials for therapeutic approval in uveal melanoma where benchmarks are clearly surpassed compared with historic reports with confirmation in a randomized study. In light of the National Comprehensive Cancer Network guidelines noting trametinib as a treatment option and recent reports citing nivolumab in combination with ipilimumab with activity (17), these agents could be considered the control arms for a randomized trial design.

In addition to uveal melanoma, the treatments discussed here may also have general implications to extend survival of patients with liver metastases such as colorectal and pancreatic cancers and/or immunologically “cold” tumors. Preclinical studies showing the role of liver stromal-derived hepatocyte growth factor (HGF) and FGF mediates targeted therapy resistance (18, 19) may have implications for other cancer types that metastasize to the liver. In uveal melanoma, however, key challenges include smaller patient cohorts due to rarity of uveal melanoma and development of therapeutic resistance. Translational research using combination of patient samples from trials and appropriate preclinical and animal models is therefore warranted.

Molecular Determinants in Uveal Melanoma

In the Basic Science session chaired by Dr. Andrew Aplin (Thomas Jefferson University, Philadelphia, PA), novel findings about the biology and mutations in uveal melanoma (*GNAQ/11*, *BAP1*), strategies for targeting key pathways (Fig. 1), and future needs for research were discussed previously (20, 21). Dr. William Harbour (Bascom Palmer Eye Institute, Miami, FL) spoke on the key role of *BAP1* loss in transcription factor networks. *BAP1* promotes progenitor cell differentiation into melanocytes by increasing microphthalmia-associated transcription factor (MITF) expression and *BAP1* loss may promote metastasis in uveal melanoma by remodeling the epigenome to resemble that of stem-like migratory neural crest cells. While *BAP1* is likely to display context-dependent functions, a more detailed understanding of its role in uveal melanoma will impact malignant mesothelioma and renal cell carcinoma (RCC) given its frequent mutation in these cancer types. *BAP1* also functions as a tumor suppressor in these tumors. *BAP1* knockout in mice leads to malignant mesothelioma growth, larger tumors, and increased number of metastases and *BAP1* protein expression is also correlated with poor prognosis and shorter survival in RCC and cholangiocarcinoma, as well as uveal melanoma (22–25). Dr. Hunter Shain (University of California San Francisco, San Francisco, CA) presented about sequencing paired primary and metastatic tumors from 35 patients. He posited that *Gαq/11* mutations undergo selection early in uveal melanoma followed by *BAP1* loss and then gain of chromosomal arm 8q in evolution to metastasis (26). A striking observation is that uveal melanoma metastases display more mutations and genomic alterations compared with primary tumors, a feature that is unique to uveal melanoma. A future avenue will be to determine whether *BAP1* loss, 8q gain, or additional late-stage alterations offer therapeutic opportunities.

Dr. Michael Onken (Washington University, St. Louis, MO) presented data on the cyclic depsipeptide, FR900359, a Gαq inhibitor which shifts and traps Gαq into a GDP-bound (inactive) state (27). Ongoing questions regarding Gαq inhibitors are whether they will be sufficient to elicit durable responses in liver metastatic *in vivo* uveal melanoma models and the tolerability of these agents. The

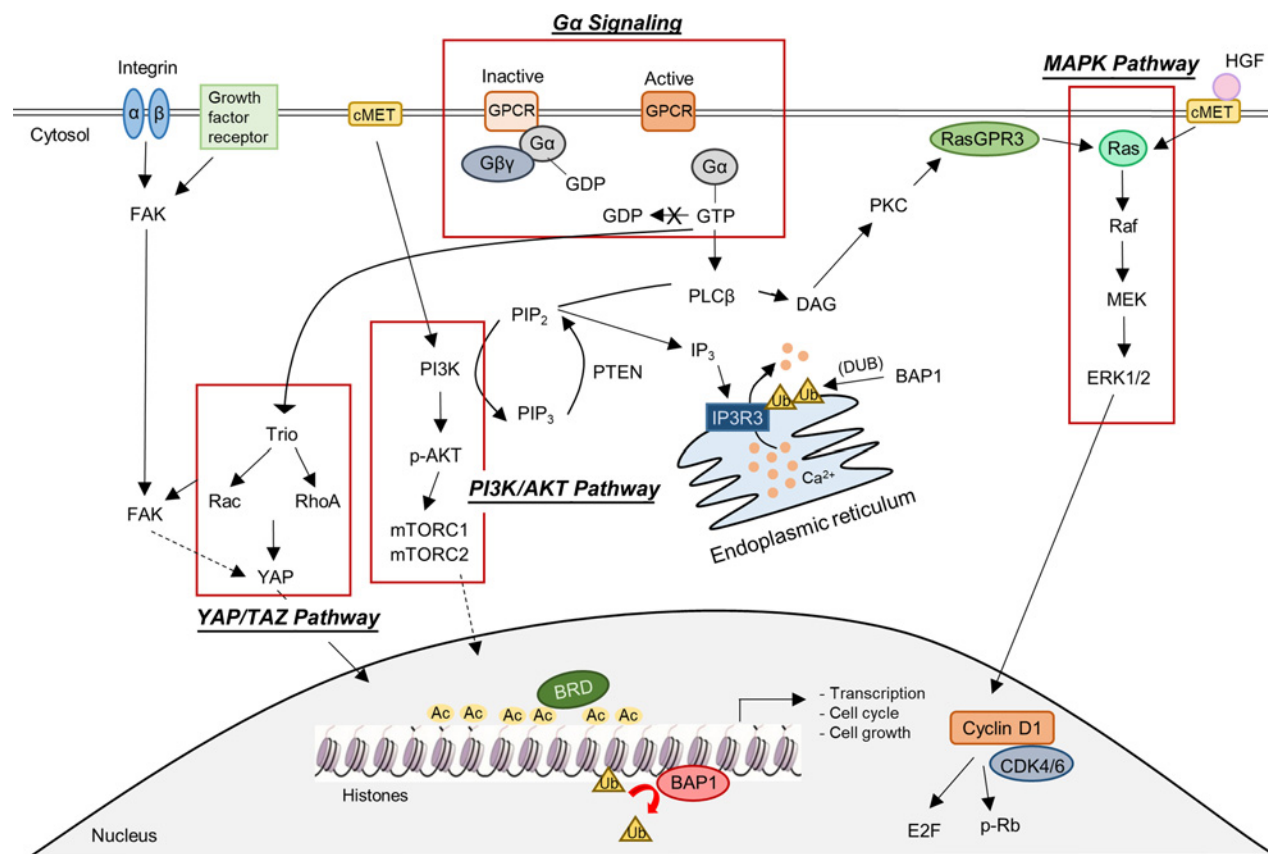


Figure 1.

Cross-talk between key and emerging signaling pathways that are therapeutically targetable in uveal melanoma. Key pathways in uveal melanoma include the G α signaling and its downstream cascades, such as the MAPK (MEK/ERK), YAP/TAZ, and PI3K/AKT pathways. The MAPK and PI3K/AKT pathways are also activated by the HGF and its receptor, cMET. Cyclin D1 and CDK4/6 are downstream of ERK1/2. FAK is often activated by integrins or growth factor receptors [e.g., PDGFR (PDGFR) and EGFR] and directs signals, in part, through YAP/TAZ. These pathways ultimately regulate gene transcription, cell growth, and cell-cycle progression. Major roles of BAP1 in the nucleus and cytoplasm are also shown. BAP1 has been shown to deubiquitinate histones in the nucleus and also the calcium transporter, IP3R3, on the endoplasmic reticulum. The BET protein, BRD4, binds to acetylation of histones and regulates gene transcription and is also a druggable therapeutic target in uveal melanoma.

development of more selective inhibitors would be a major advance for the field. These studies with G-protein inhibitors will also likely impact skin melanoma and other nonmelanoma cancers that harbor G-protein coupled receptor (GPCR) alterations such as meningeal, biliary tract, and lung tumors (28). Ms. Amanda Truong (University of Utah, Salt Lake City, Utah) showed that combination of an autophagy inhibitor, hydroxychloroquine with a MEK inhibitor, synergistically delays *GNAQ/11* mutant uveal melanoma growth. These findings extend previous observations in pancreatic cancer where MEK inhibitors induce autophagy, which was also seen in uveal melanoma (29). Dr. Keiran Smalley (Moffitt Cancer Center, Tampa, FL) showed activation of oncogenic pathways such as PI3K/AKT and YAP/TAZ following MEK inhibitor treatment of *GNAQ/11* mutant uveal melanoma cell lines, with the pathways and uveal melanoma growth *in vitro* and *in vivo* further inhibited by combining MEK and histone deacetylase inhibitors (30). The next step for this combination is to determine whether *BAP1* status influences the response and its translational testing in both the high-risk adjuvant and metastatic settings. These findings will add to our understanding of crosstalk between the MAPK and compensatory pathways, as well as, combination therapeutic strategies involving

MEK inhibitors that could be tested in melanomas as well as in cancers driven by the MAPK pathway (31). Whilst preclinical *in vitro* findings seem promising, a challenge in uveal melanoma research is the lack of representative animal models. At this meeting, we learnt about a zebrafish model for uveal melanoma by Ms. Grace Phelps (Massachusetts Institute of Technology, Cambridge, MA) who showed that expression of *GNAQ* Q209L leads to tumor growth which was accelerated by a concomitant loss of *MITF* (32).

Novel Targets in Uveal Melanoma

The Novel Targets session, chaired by Richard Carvajal (Columbia University, New York, NY), covered new targets (Fig. 1) in uveal melanoma that are likely translated to clinical trials. Dr. Stefan Kurtenbach (Bascom Palmer Eye Institute, Miami, FL) presented functions of PRAME (33), which is associated with aggressive forms of uveal melanoma but its functional contribution in uveal melanoma is not well understood. Dr. Kurtenbach showed that PRAME expression maintains cells in a stem-like state, is associated with chromosomal instability and aneuploidy in uveal melanocytes, suggesting that

PRAME is not just a biomarker but a promoter of uveal melanoma metastasis.

Dr. Grazia Ambrosini (Columbia University, New York, NY) presented on BRD4, a bromodomain and extraterminal (BET) protein (34, 35). The combination of BET inhibitors and MEK inhibitors induces synergistic growth inhibitory on uveal melanoma growth and is currently being proposed for a clinical trial. Next-generation BET inhibitors such as PLX2853 (NCT03297424), have been developed and their shorter half lives may overcome the tolerability of first-generation BET inhibitors and enable combination studies in uveal melanoma and other cancers.

Ms. Nadia Arang (University of California San Diego, San Diego, CA) showed that focal adhesion kinase (FAK) is a druggable therapeutic target in uveal melanoma. The combination of FAK and MEK inhibitors synergistically promotes apoptotic cell death and reduces tumor burden *in vivo*. This study underscored the utility of synthetic lethality screens to identify for precision oncology. The FAK inhibitor, defactinib, has been combined with the MEK inhibitor, VS-6766, in several cancers (NCT03875820) and in uveal melanoma, FAK/MEK cotargeting is slated to start investigation clinically in 2020.

Dr. Prabhjot Mundi (Columbia University, New York, NY) discussed the OncoTreat clinical pipeline which is a reconceptualization of cancer as orchestrated chaos. OncoTreat identifies aberrantly activated nodes and profiles the effects of different drugs on nodal activity. A future goal is to apply this platform to uveal melanoma and further develop *in vivo* models such as patient-derived xenografts (PDX) in which predictions can then be validated. Dr. Moony Tseng (The Broad Institute) talked about the Cancer Cell Line Factory and Cancer Dependency Map (<https://depmap.org/portal/>) whose goal is to identify rare tumor vulnerabilities using the drug repurposing library and genome-scale CRISPR screens. Patients with rare tumor diseases in United States and Canada can donate fresh tissue to support the generation of laboratory models that can be widely shared.

Summary and Future Directions

Uveal melanoma is biologically and clinically distinct from cutaneous melanoma and, regardless of the success of primary tumor therapy, about 50% of patients experience metastasis (2, 36). The outcome of patients with metastatic disease remains discouraging with a median survival after metastasis of 12 months (37–39). The MRF CURE OM Science Meeting highlighted increased efforts in preclinical and translational research with dedicated uveal melanoma clinical trial opportunities.

The inclusion of patients with uveal melanoma in clinical trials early in the drug development process is critical to accelerate access to active therapies. In the Clinical Trials session at the meeting, several of the studies focused on strategies to improve the efficacy of liver-directed therapies and immune checkpoint inhibitors. The management of liver metastases from uveal melanoma continues to be a significant challenge and there is little consensus on how to manage this other than recommendations for participation on a clinical trial (https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf). Studies suggest regional liver-directed therapy may achieve disease control that is more durable than that achieved with the available systemic therapeutic options (40, 41). But increasing survival benefit warrants innovation in terms of strategies to overcome immune resistance such as promotion of a type I IFN response. Intratumoral approaches are underway to promote this mechanism. Tebentafusp is a leading candidate to make inroads into uveal melanoma survival via T-cell redirection. The ideal patient population (treatment-naïve, post-

checkpoint blockade) to benefit from this therapy is being further delineated. Translational studies of responders versus nonresponders will be critical to our understanding of how these class of agents provide benefit, produce toxicity, and redirect the immune system.

Several research groups have identified evolutionary events in genetic and chromosomal alterations in uveal melanoma tumors from pretumorigenic lesions to metastases, leading us to further understand the role of key molecular determinants in driving uveal melanoma development and progression. Key questions to address relate to the heterogeneity of primary tumors versus metastatic alterations. Single-cell sequencing data will also further characterize the immune cell populations present in uveal melanoma. Basic science advancements have uncovered mechanisms of mutant $G\alpha q/11$ signaling, MEK1/2 resistance via autophagy, and compensatory pathway signaling with direct therapeutic implications. An important development for targeted therapy strategies in uveal melanoma would be the generation of selective YAP/TAZ-TEAD pathway inhibitors and their testing in uveal melanoma models given the evidence for this pathway playing a key role downstream of mutant $G\alpha q/11$ signaling. These druggable therapeutic clues must now be pursued in the clinic in well-designed studies. Targeted therapy with second-generation PKC inhibitors is also being investigated and translational research on compensatory pathway activation is imperative to further this agent in combinatorial approaches. Progress is on the horizon as a number of novel targets are making their way into clinical trial development. PRAME as a target is being addressed in at least two trials to increase T-cell recognition of this antigen (NCT03686124, NCT04262466). BET inhibitors have been studied and are being proposed in combination with MEK inhibition due to evidence of preclinical synergy. FAK inhibition as monotherapy and in combination with MEK inhibition is a novel clinical trial that opened for enrollment in the year 2020. As these and other targeted therapy strategies also reach the clinic preclinical modeling and patient sample material should be carefully paired to define characteristics of drug-tolerant persister cells and mechanisms of therapy resistance. Comparison of uveal melanoma with cancers that are molecularly similar will be important in future studies such as by analysis of epigenetics, metabolic profiles, and their plasticity. There is an ongoing project studying adenosine signaling and immune suppression in uveal melanoma and pancreatic adenocarcinoma. However, differences may exist. For example, malignant mesothelioma cells are more sensitive to EZH2 inhibitors following loss of *BAP1* but this has not been shown in uveal melanoma (42). These studies could also lead to context-selective discovery of novel therapeutic strategies and understanding whether *BAP1* loss promotes metastasis.

High-throughput and large-scale tools such as OncoTreat and the Cancer Cell Line Factory are key instruments in helping predict drug-augmented pathways and provide a tumor dependency map. We must carry on contributions to these important model generating systems with patient-derived tumor tissue to increase our understanding of mechanisms driving metastatic uveal melanoma. *In vivo* models for uveal melanoma need continued refinement with key insights emerging from zebrafish and chick chorioallantoic membrane models (32, 43). Zebrafish models are important given their application to high-throughput screen and that they can be used in large numbers, supporting statistical analysis. Another need in the field is for a mouse model that faithfully represents the genetic and biological features of uveal melanoma. Such a model would enable preclinical testing of immune-based therapies. Additional PDX models that represent the diversity of uveal melanoma both at the genetic level are also required.

The information presented at this meeting showed that there has been progress in uveal melanoma research on the clinical trials, basic science, and novel targets fronts. These advancements would not have been possible without a multidisciplinary team invested in optimizing outcomes for patients with uveal melanoma, and the combined efforts of philanthropy, the organizers at the MRF (Washington, DC), and the uveal melanoma patient community.

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